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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: L-glufosinate-Ammonium (Ignite[R]; Hoe 058192): Review of acute and developmental toxicity studies

Caswell No. 580I **PC Code:** 128850
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The registrant, AgrEvo (A Co. of Hoechst and NOR-AM), submitted 4 acute toxicity studies and a developmental toxicity study on l-glufosinate ammonium. These studies have been reviewed. The Data Evaluation Record for each study is attached. The citation and conclusion for each study are presented below:

1. Diehl, K. -H. and Leist, K. -H. (1988). Hoe 058192-active ingredient technical (Code: Hoe 058192 OH ZC88 0001): Testing for acute oral toxicity in the male and female Wistar rat. Pharma Research Toxicology and Pathology, Hoechst Aktiengesell-schaft, Germany; Study No.: 88.0180. Feb. 22, 1988. Submitted to US EPA by AgrEvo[TM]; MRID No. 43829401. Unpublished.

In this study groups of Wistar rats (5/sex/group) received a single oral dose of L-glufosinate (88.2% a.i.) by gavage at doses ranging from 500 to 3150 mg/kg b.w. and were observed daily for 14 days.

Oral LD_{50} Males = 709 mg/kg
Females = 669 mg/kg

The acute oral toxicity category for Hoe 058192 in rats is III based on the LD_{50} in females (669 mg/kg b.w.). There were treatment-related clinical signs which included disturbance of body postures, movement (ataxia), and spontaneous activities (reduced). Furthermore, spasms, agitation, miosis, and an impairment of respiration were reported. This acute oral study in rats (81-1) is classified as **acceptable**.

2. Diehl, K. -H. and Leist, K. -H. (1988). Hoe 058192-active ingredient technical (Code: Hoe 058192 OH ZC88 0001): Testing for acute oral toxicity in the male and female NMRI mouse. Pharma Research Toxicology and Pathology, Hoechst Aktiengesell-schaft, Germany; Study No.: 88.0181. March 1, 1988. Submitted to US EPA by AgrEvo™; MRID No. 43829402. Unpublished.

In this study, groups of NMRI mice (5/sex/group) received a single oral dose of L-glufosinate (88.2% a.i.) by gavage at doses ranging from 125 to 800 mg/kg b.w. and observed daily for 14 days.

Oral LD_{50} Males = 137 mg/kg
Females = 122 mg/kg
Combined = 129 mg/kg

The acute oral toxicity category for Hoe 058192 in mice is II based on the combined LD_{50} (129 mg/kg b.w.). There were treatment-related clinical signs which included disturbance of body postures, movement (ataxia), and spontaneous activities (reduced). In addition, spasms, agitation, miosis, and an impairment of respiration were seen. This acute oral study in mice (81-1) is classified as **acceptable**.

3. Diehl, K. -H. and Leist, K. -H. (1988). Hoe 058192-active ingredient technical (Code: Hoe 058192 OH ZC88 0001): Testing for acute intraperitoneal toxicity in the male and female Wistar rat. Pharma Research Toxicology and Pathology, Hoechst Aktiengesell-schaft, Germany; Study No.: 88.0185. Aug. 4, 1988. Submitted to US EPA by AgrEvo™; MRID No. 43829403. Unpublished.

In this study, groups of Wistar rats (5/sex) received a single oral dose of L-glufosinate (88.2% a.i.) by i.p. at doses ranging from 10 to 800 mg/kg b.w. and observed daily for 14 days. **Oral LD_{50} Males = 94.9 mg/kg**
Females = 20.5 mg/kg

There were treatment-related clinical signs which included disturbance of body

postures, movement (ataxia), and spontaneous activities (reduced). In addition, spasms, agitation, miosis, and an impairment of respiration were seen. This acute peritoneal study in rats is classified as **acceptable**. An acute toxicity study with intraperitoneal administration is not required by the Agency, and a toxicity category classification scheme for this type of study is not available. However, if the toxicity classification for acute oral study were to be used, under the conditions of this study the toxicity category for this chemical would be I based on the LD_{50} (20.5 mg/kg b.w.) in female rats.

4. Hoffman, TH. and Jung, R. (1988). Hoe 058192-active ingredient technical (Code: Hoe 058192 OH ZC88 0001): Testing for acute dust inhalation toxicity in the male and female SPF Wistar rats-4-hour LC_{50}. Pharma Research Toxicology and Pathology, Hoechst Aktiengesell-schaft, Germany; Study No.: 88.0187. April 20, 1988. Submitted to US EPA by AgrEvo™; MRID No. 43829404. Unpublished.

Groups of young adult SPF Wistar rats (5/sex) were exposed by inhalation route to Hoe 058192 (88.2% a.i.) for 4 hours to nose only at concentrations of 0.051, 0.116, 0.175, 0.202, 0.293 or 0.659 mg/L. Animals then were observed for 14 or 21 days.

LC_{50} males = 0.138 mg/L
Females = 0.314 mg/L

Hoe 058192 is TOXICITY CATEGORY II, based on values of the LC_{50} for males and females which are less than 0.5 mg/L and greater than 0.05 mg/l. The clinical signs included uncoordinated gait, red nasal discharge, hunched posture, stilt gaits, miosis,irregular breathing, piloerection, drowsiness, delayed righting reflex, ataxia, pinch- and corneal reflex, narrowed palp. fissures, and encrusted eye and snout. Irregular breathing was seen 5 minutes after the treatment began and, some clinical signs persisted till the termination of the study.

This acute inhalation study is classified as **acceptable**. It satisfies the guideline requirement for an acute inhalation study (81-3) in the rat.

5. Becker, H., Biedermann, K., and Terrier, Ch. (1992). Embryotoxicity study (including teratogenicity) with Hoe 058192 substance technical (Code: Hoe 058192 OH ZC88 0002) in the rabbit. RCC, Research and Consulting Co. Ltd., Switzerland and RCC UMWELTCHEMIE AG. Switzerland; Study No.: 207257. May 22, 1992. Submitted to US EPA by AgrEvo™; MRID No. 43829405. Unpublished.

In this study, groups of mated Chinchilla rabbits (16/dose group) received Hoe 058192 (88.2% a.i.) by gavage at dose levels of 1.25, 2.50, and 5.00 mg/kg/day

from gestation days 6 to 18 inclusive. In the high dose group (5.00 mg/kg), one treatment-related death occurred, and prior to death this dam showed clinical signs of severe spasms, lateral recumbency, and muscle twitching. In addition two other high dose dams also exhibited signs of abortion; these two dams were sacrificed prior to termination of the study. A dose-related decrease in body weight gain and food consumption was seen in the mid and high dose dams. The absolute kidney weights in the high dose dams were increased. **Based on the decrease in body weight gains and food consumption, neurotoxic signs, and abortions, the LOEL and NOEL for maternal toxicity were 2.5 and 1.25 mg/kg, respectively.**

A statistically significant increase in post-implantation loss/fetal resorptions was found in mid and high dose groups. No increases in the incidence of external, visceral or skeletal malformations or skeletal variations (altered growth) were found. **The LOEL for developmental toxicity is 2.5 mg/kg based on an increase in post-implantation loss (fetal resorptions); NOEL, 1.25 mg/kg.**

This study is classified as **acceptable** and satisfies the guideline requirements for a developmental toxicity study in rabbits (§ 83-3b).

A comparison of the toxicity between the DL-glufosinate ammonium and the L-glufosinate ammonium is shown in Table 1. Based on the data in this submission, the purified L-glufosinate ammonium is more toxic. This finding is consistent because the L-isomer is the active form of this chemical.

Table 1: Comparative toxicity of DL- and L-glufosinate ammonium[a]

Study Type	mg/kg[+]	
	DL-GFA[*]	L-GFA[*]
Rat oral LD_{50} (male/female)	2000/1620	709/669
Mouse oral LD_{50} (male/female)	431/417	137/129
Rat intraperitoneal LD_{50} (male/female)	96/83	95/20
Rat inhalation LC_{50} (male/female) (mg/L)	1.26/2.60	0.139/0.314
Developmental toxicity-rabbit (NOEL: maternal/developmental)	10/50	1.25/1.25

a: The data for DL-glufosinate ammonium are excerpted from the HED One-liner and the submission.
+: For the rat inhalation study the unit is mg/L.
*: DL-GFA=DL-glufosinate ammonium (Hoe 039866); L-GFA=L-glufosinate ammonium (Hoe 058192).

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